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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/862,571	05/21/2001	Glenn McGall	2719.2019-001	9482

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EXAMINER

BORIN, MICHAEL L

ART UNIT

PAPER NUMBER

1631

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/862,571

Applicant(s)

MCGALL ET AL.

Examiner

Michael Borin

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) 4, 5, 8, 10 and 11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 6, 7, 9, 12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/11/2003 has been entered.

Status of the claims

2. Claims 1-12 are pending.

During the prosecution of the application, applicant elected, without traverse, Group I, claim 3, together with linking claims 1,2,6-9,12. Claims 4,5,8,10,11 remain withdrawn from consideration. Further, in regard to election of species, applicant elected photolabile protecting groups, and compound of Formula II. Claims reading on the elected species are 1-3,6,7,9,12. Claims 1-3,6,7,9,12 are addressed to the extent they read on the elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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3. Claims 1-3,6,7,9,12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. First, the claims remain rejected for the reasons of record. It is not clear how use of phosphoramidate (such as elected species of formula II) will result in formation of phosphate. The claims, as drawn to elected species (see claim 9), are drawn to replacing an oligonucleotide protective group with a negatively charged phosphate group by removing protective group and reacting thus formed active site with a phosphoramidite of formula II.

Phosphate, according to a dictionary definition is a

$(\text{PO}_4)^{-3}$ ion, or a compound comprising $(\text{PO}_4)^{-3}$

(see, e.g., on-line Webster Dictionary,
<http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=phosphate>).

Then, it is not clear how a compound of Formula II, which a) have different valency, and b) do not have negatively charged groups, can introduce $(\text{PO}_4)^{-3}$ group as claimed.

Applicant, again, argues that it is well known in the art that phosphoramidates can readily be reacted to form phosphate groups. In support, applicant refers to Appendices A-C filed together with the response of 12/11/2003 – no direction to any particular section of these references is provided, however.

Upon cursory examination of the references, examiner finds support for his, rather

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than applicant's position. Thus, the slides of the presentation of Dr. Curran (Appendix A) clearly distinguish between phosphites and phosphates (see slides #7,8), show that routine use of phosphoramidite method (i.e., using compounds addressed in the instant claims) in nucleotide chemistry does not lead to phosphates (see slides #14,15,17,18) and that conversion of phosphates to phosphates requires special conditions and reagents allowing oxidation of phosphates (slide #16). The latter conditions are not described or meant in the instant specification.

Appendix "B" (Finney reference), again, shows that phosphate esters (not negatively charged phosphate groups) are generated from phosphates by oxidation reaction. Appendix "C" does not address the issue.

Examiner agrees with applicant's position that an artisan would immediately recognize that the use of the claimed reagent would lead to a phosphite ester. Examiner disagrees, however, with applicant's statement that hydroxyl group could be reacted with phosphotriester to form a phosphate residue – it will either not react at all, or, at best, form another phosphotriester. Examiner maintains that neither the claims, nor specification address conversion of phosphates into phosphates and all that the instant claims require is addition of phosphoramidate as a terminal group to an unprotected nucleotide.

B. As the claims are amended to remove term "target molecule" (reduction of non-specific binding of which is the purpose of the method according to

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specification), it became not clear non-specific binding of what is the objective of the method.

C. Claim 1 b) ii) lacks internal antecedent basis as it recites "said target molecule" – the term "target molecule" is absent in the preceding claim language.

Claim Rejections - 35 USC § 112, first paragraph.

4. Claims 1-3,6,7,9,12 are rejected under 35 U.S.C. 112, first paragraph, as based on specification which is not enabling. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims, as drawn to elected species (see claim 9), are drawn to reducing non-specific binding to an oligonucleotide chip by replacing an oligonucleotide protective group with a negatively charged phosphate group by removing protective group and reacting thus formed active site with a phosphoramidite of formula II. First, there is no showing of how to deliver a negatively charged phosphate group by interacting active site with a phosphoramidite of formula II – see rejection under 35 U.S.C. 112, second paragraph above.

Second, the specification does not provide support for the claimed effect of reducing non-specific binding by introducing negatively charged phosphate

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groups. The only example present in specification demonstrates reduction of binding of a specific protein, namely fluorescent protein conjugate phycoerythrin-streptavidin (Example 1¹). The non-specific background binding does not significantly change with introduction of a phosphate group (compare second and forth rows of Table I, where "m" changes from 0 to 1). The claimed method is supposed to work on arrays testing biological samples. A biological sample is blood, urine, tissue, etc. As any of the molecules present in such sample is capable of binding to the surface of the array, the question is whether specification describes or provides guidance for the claimed universal effect of the negatively charged phosphate residues against non-specific binding of any of plethora of molecules capable of non-specific binding.. Evidently, biological samples contain plethora of molecules differing both in their chemical activity (i.e., with different affinity to react with phosphate group), and charge (i.e., negatively or positively charged). Thus, any positively charged molecule, e.g. a positively charged protein, would be attracted, rather than repulsed by the negative charge of the phosphate group, the effect that would increase rather than decrease non-specific binding. Specification does not provide any guidance on how to achieve reduction of binding by replacing an oligonucleotide protective group with a negatively charged phosphate group, even less so for the instance wherein phosphate group is introduced by removing protective group and reacting thus formed active site

¹ Note that Example 1 does not illustrate the elected embodiment of the method.

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with a phosphoramidite of formula II. Prior art teaches phosphoroamidites as oligonucleotide functionalizing reagents (see, e.g., US Patent 4,914,210) but do not teach that these compounds "reduce non-specific binding of a target molecule".

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Response to arguments

Applicant points at Table II as supporting the method as claimed, and asserts that "the specular background was almost completely eliminated when a number of negatively charged phosphate residues was included throughout oligonucleotide array" (p. 11, last full paragraph of the response). Examiner disagrees. Table 2 illustrates effect of increase in parameter "n", which, unlike parameter "m", does not include phosphate groups (see specification, p. 42, bottom). Further, applicant alleges that Table 2 demonstrates decreases binding of "insoluble metal salts". Examiner failed to identify discussion of binding of "insoluble metal salts" in the discussed section of specification. Furthermore, applicant, surprisingly, declares that the feature shared by "insoluble metal salts" and "most proteins" is a "hydrophobic or negatively charged surface", and by due to such characteristic

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negatively charged phosphate group can be easily recognized as capable of reducing non-specific binding. Examiner questions scientific reasoning behind both of these statements and invites applicant to provide references confirming their validity.

5. Claims 6,7,9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 6, item 2), introduces new matter as they it uses phrase use the phrase "one or more compounds".

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

mlb